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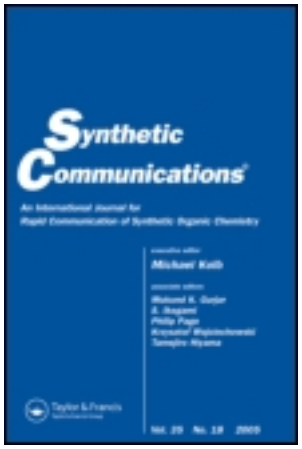

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Synthesis and Characterization of Some New Benzimidazole Derivatives

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SYNTHESIS AND CHARACTERIZATION OF SOME NEW BENZIMIDAZOLE DERIVATIVES

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Synthesis of nine new benzimidazole derivatives was reported. The products were identified by ^{1}H NMR, mass spectroscopy, and infrared spectroscopy.

Keywords: Anti-inflammatory; anti-ulcerative; derivatives of benzimidazoles; synthesis and characterization

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INTRODUCTION

Benzimidazole derivatives have been found to possess a wide range of biological activities, such as anticonvulsant,[1] antidepressant,[2] antihistamine,[3,4] antifungal,[5] antihypertensive,[6] anticancer,[7] anti-inflammatory,[8] anthelmintic,[9,10] and antiallergic[11] properties. The biological activities of the compounds containing this basic moiety have been well documented.[12] Some of them (such as thiabendazole, mebendazole, and albendazole) are widely used as antihelmintic drugs.[13] Similarly, benzimidazole-2-thiol and its derivatives have also been reported to have potent biological activities, such as proton pump inhibitory activity,[14] antiulcer activity,[15] and potassium-activated ATPase (H^+/K^+-ATPase) inhibitory activity.[16]

The therapeutic agents that have been commonly used for the treatment of ulcers are antacids for neutralizing gastric acid, antipepsin agents for protecting the gastric mucous membrane, and anticholinergic agents for inhibiting gastric acid secretion.

At the present time, histamine-H2 receptor antagonists have been widely used for treating gastric and duodenal ulcers. More recently, proton pump inhibitors are gaining importance because they block the proton pump of the H^+/K^+-ATPase enzyme specifically present in the parietal cells of the stomach and inhibit the gastric acid secretion at the final stage.

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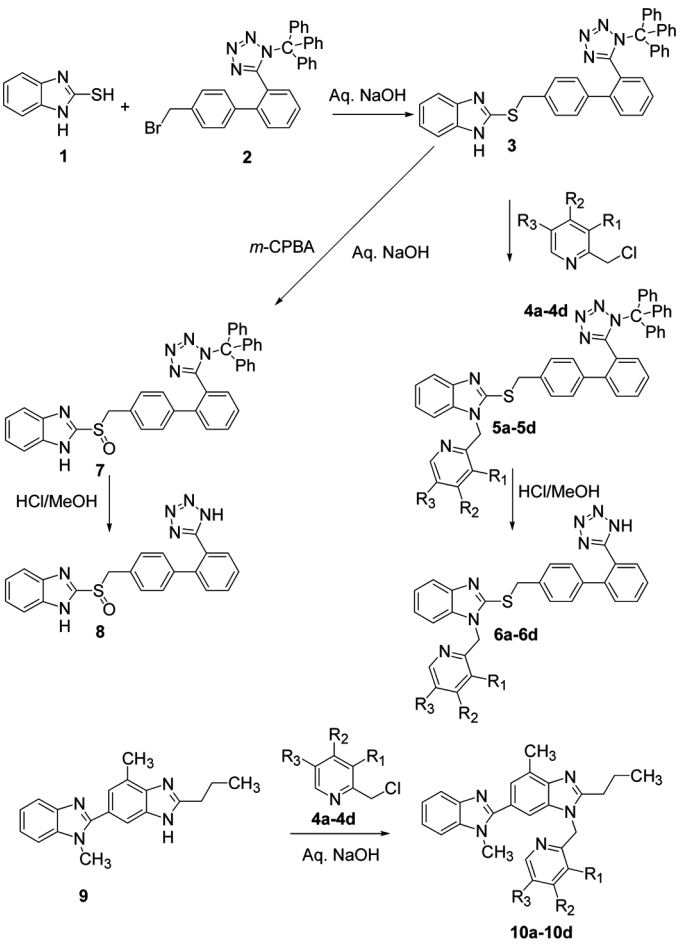

	R1	R2	R3
4a, 5a, 6a, 10a=	CH_3	OCH_3	CH_3
4b, 5b, 6b, 10b=	OCH_3	OCH3	H
4c, 5c, 6c, 10c=	CH_3	OCH_2CF_3	H
4d, 5d, 6d, 10d=	CH_3	$OCH_2CH_2CH_2OCH_3$	H

Scheme 1. Synthesis of benzimidazole derivatives.

Ganser and Forte were the first to demonstrate that parietal cell membranes contain a H^+/K^+-ATPase enzyme, which operates as a proton pump. Substituted benzimidazoles are capable of blocking gastric acid secretion in response to known stimuli. It is reported that benzimidazole sulfide is capable of inhibiting gastric acid secretion in vivo.

In view of the biological and pharmacological importance of both pyridine and benzimidazole moieties, it was thought worthwhile to synthesize new benzimidazole derivatives coupled with both pyridine and benzimidazole moieties.

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RESULTS AND DISCUSSION

Three series of benzimidazole derivatives containing both pyridine and benzimidazole moieties are prepared. One series of benzimidazole derivatives was prepared as follows:

The reaction of 2-mercapto-1*H*-benzimidazole (**1**) with 4′-bromomethyl-biphenyl-2-tetrazole (**2**) in aqueous sodium hydroxide at room temperature gives product **3**. Compound **3** is reacted with 2-chloromethyl pyridine derivatives **4a–d** in the presence of aqueous sodium hydroxide at room temperature to afford compounds **5a–d**. The compounds **5a–d** are treated with aqueous hydrochloric acid in the presence of methanol to give products characterized as compounds **6a–d** on the basis of spectral and analytical data. Thus, IR spectra showed characteristic absorptions at 3400 cm^{-1} (assignable to the tautomeric NH-group of the imidazole), 3050 cm^{-1} (assignable to the aromatic C−H stretching), around 1630 and 1580 (assignable to the aromatic C=C, C=N stretching), 1460 strong band (assignable to the aliphatic C−H bending), and 1070 (assignable to the C−O stretching). The IR, ^{1}H NMR, and mass spectra are mentioned in the Experimental section.

The other series of benzimidazole was prepared by sulfoxidation of **3** with meta-chloroperbenzoic acid (*m*-CPBA) in dichloromethane (DCM) to give compound **7**. The compound **7** is deprotected with aqueous hydrochloric acid in the presence of methanol to yield compound **8**, which was characterized on the basis of its spectral and analytical data. Thus, its IR spectrum showed characteristic absorption at 3420 cm^{-1} (assignable to the tautomeric NH group of the imidazole ring), 3050 cm^{-1} (assignable to the aromatic C−H stretching), around 1600 and 1580 (assignable to the aromatic C=C, C=N stretching), and 1476 (assignable to the aliphatic C−H bending). Its IR, ^{1}H NMR, and mass spectra are mentioned in the Experimental section.

The another series of benzimidazoles were prepared by treating of **9** with **4a–d** in the presence of aqueous sodium hydroxide at 50 °C for 15 h at room temperature to give the products characterized as compounds **10a–d** on the basis of spectral and analytical data. The IR spectra showed absorption around 3050 cm^{-1} (assignable to the aromatic C−H stretching), around 1580 and 1560 (assignable to the aromatic C=C, C=N stretching), 1460 (assignable to the aliphatic C−H bending), and 1035 (assignable to the C−O stretching). Its IR, ^{1}H NMR, and mass spectra are mentioned in the Experimental section. See Scheme 1.

EXPERIMENTAL

The IR spectra were recorded in the solid state as KBr dispersion media using a Perkin-Elmer Spectrum One Fourier transform (FT)–IR spectrophotometer. ^{1}H NMR was recorded in dimethylsulfoxide (DMSO) using a 400-MHz Varian Mercury Plus 400-MHz FT NMR spectrometer in DMSO-d_6. The ^{1}H chemical shift values were reported on the δ scale in parts per million, relative to tetramethylsilane (TMS; δ = 0.00 ppm). The liquid chromatography–mass spectrometry (LC-MS) was performed on a AB-4000 Q-trap LC-MS/MS mass spectrometer. Compounds **1, 2**, and **4a–d** were procured from Dr. Reddy's Laboratories Ltd., Hyderabad, India.

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Preparation of 6a–d from 1 and 2 (General Procedure)

2-Mercapto-1*H*-benzimidazole (**1**) (14 g, 0.093 mol) and 1-bromomethyl biphenyl tetrazole (**2**) (50 g, 0.089 mol) were added to a solution of sodium hydroxide (30 g, 0.75 mol) in water (150 mL) and acetone (1000 mL) at 25–30 °C. The reaction mass was stirred for 15 h and concentrated, followed by isolation of the product **3** in water (200 mL). Yield 48 g (85%).

Compounds **3** (40 g, 0.063 mol) and **4a–d** (0.063 mol) were added to a solution of sodium hydroxide (24 g, 0.6 mol) in water (120 mL) and acetone (800 mL) at 25–30 °C. The reaction mass was stirred for 15 h and concentrated, followed by isolation of the products **5a–d** from water (160 mL). Yield: 85%.

A solution of 36% HCl (50 mL, 15 mol) was added to a solution of compounds **5a–d** (25 g) in methanol (200 mL) at 10–15 °C and stirred for 1 h. The separated by-product (trityl chloride) was filtered and charged with water (500 mL). The resulting solution was stirred for solid separation and filtered to yield the hydrochloride salts **6a–d**. Yield: 65%.

Data for Compounds 6a–d

Compound 6a. ^{1}H NMR δ 7.96 (s, 1H), 7.59 (d, $J = 8$ Hz, 1H), 7.52 (d, $J = 6.8$ Hz, 1H), 7.31 (m, 4H), 7.18 (d, $J = 8$ Hz, 1H), 7.12 (m, 4H), 7.02 (d, $J = 7.6$ Hz, Hz, 1H), 5.38 (s, 2H), 4.49 (s, 2H), 3.71 (s, 3H), 2.24 (s, 3H), 2.13 (s, 3H); MS m/z 534 ($M^+ + H$); FT-IR (KBr, cm^{-1}): 3435 (N−H stretching), 3050 (aromatic C−H stretching), 2960 (aliphatic C−H stretching), 1638, 1580 (aromatic C=C, C=N stretching), 1460 (aliphatic C−H bending), 1071 (C−O stretching), 760, 744 (aromatic C−H bending).

Compound 6b. ^{1}H NMR δ 8.03 (d, $J = 5.6$ Hz, 1H), 7.57 (d, $J = 6.8$ Hz, 1H), 7.52 (d, $J = 5.2$ Hz, 1H), 7.29 (m, 6H), 7.15 (m, 4H), 7.03 (d, $J = 5.6$ Hz, 1H), 5.41 (s, 2H), 4.53 (s, 2H), 3.86 (s, 3H), 3.73 (s, 3H); MS m/z 536 ($M^+ + H$); FT-IR (KBr, cm^{-1}): 3392 (N−H stretching), 3058 (aromatic C−H stretching), 2974 (aliphatic C−H stretching), 1637, 1585 (aromatic C=C, C=N stretching), 1459 (aliphatic C−H bending), 1070 (C−O stretching), 762, 748 (aromatic C−H bending).

Compound 6c. ^{1}H NMR δ 8.16 (d, $J = 6$ Hz, 1H), 7.56 (m, 6H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.26 (m, 4H), 7.12 (d, $J = 6$ Hz, 1H), 7.03 (d, $J = 8$ Hz, 1H), 5.59 (s, 2H), 4.93 (q, $J = 8.4$ Hz, 16.8 Hz, 2H), 4.63 (s, 2H), 2.25 (s, 3H); MS m/z 588 ($M^+ + H$); FT-IR (KBr, cm^{-1}): 3421 (N−H stretching), 3053 (aromatic C−H stretching), 2970 (aliphatic C−H stretching), 1630, 1583 (aromatic C=C, C=N stretching), 1477 (aliphatic C−H bending), 1169 (C−O stretching), 760, 745 (aromatic C−H bending).

Compound 6d. ^{1}H NMR δ 8.03 (d, $J = 5.6$ Hz, 1H), 7.56 (m, 6H), 7.32 (d, $J = 8$ Hz, 1H), 7.11 (m, 4H), 7.01 (d, $J = 8.4$ Hz, 1H), 6.88 (d, $J = 5.6$ Hz, 1H), 5.40 (s, 2H), 4.54 (s, 2H), 4.08 (t, $J = 6.4$ Hz, 2H), 3.48 (t, $J = 6.4$ Hz, 2H), 3.24 (s, 3H), 2.19 (s, 3H), 1.96 (m, 2H); MS m/z 578 ($M^+ + H$); FT-IR (KBr, cm^{-1}): 3421 (N−H stretching), 3058 (aromatic C−H stretching), 2929 (aliphatic C−H stretching), 1630, 1582 (aromatic C=C, C=N stretching), 1478 (aliphatic C−H bending), 1087 (C−O stretching), 760, 743 (aromatic C−H bending).

Preparation of Compound 8

A solution of *m*-CPBA (11 g, 0.063 mol) in methylene chloride (100 mL) was added to a solution of compound **3** (20 g, 0.031 mol) in methylene chloride (100 mL) at 10–15 °C. The reaction mass was stirred for 1 h and filtered to yield the separated by-product (*m*-chlorobenzoic acid). The organic layer was washed the with 5% aqueous sodium hydroxide solution (2 × 100 mL). The organic layer was concentrated to dryness, and the product was isolated from acetone (20 mL) to give the compound **7**. Yield: 75%.

A solution of 36% HCl (20 mL, 0.2 mol) was added to a solution of compound **7** (10 g, 0.015 mol) in methanol (80 mL) at 10–15 °C. The reaction was stirred for 1 h, and the separated by-product (trityl chloride) was filtered. The reaction mass was concentrated to dryness, and water (200 mL) was charged. The resulting solution was stirred for solid separation, filtered, and dried in a vacuum oven to afford **8**. Yield: 65%.

Data for Compound 8

^{1}H NMR δ 7.64 (m, 4H), 7.57 (d, $J = 6.4$ Hz, 1H), 7.51 (d, $J = 8$ Hz, 1H), 7.35 (m, 4H), 7.16 (d, $J = 8.4$ Hz, 1H), 7.03 (d, $J = 8.4$ Hz, 1H), 4.68 (d, $J = 13.2$ Hz, 1H), 4.49 (d, $J = 13.2$ Hz, 1H); MS m/z 312 ($M^+ + H$); FT-IR (KBr, cm^{-1}): 3421 (N−H stretching), 3058 (aromatic C−H stretching), 2964 (aliphatic C−H stretching), 1604, 1586 (aromatic C=C, C=N stretching), 1476 (aliphatic C−H bending), 1019 (C−O stretching), 748 (aromatic C−H bending).

Preparation of Compounds 10a–d (General Procedure)

Compound **9** (25 g, 0.082 mol) and compound **4a–d** (0.082 mol) were added to a solution of sodium hydroxide (15 g 0.37 mol) in water (75 mL) and acetone (500 mL). The reaction mass was stirred for 15 h at 50 °C and concentrated. Water was charged (100 mL), followed by acetone (50 mL), and the mixture was then stirred for solid separation and filtered to yield **10a–10d**. Yield: 85%.

Data for Compounds 10a–d

Compound 10a. ^{1}H NMR δ 7.97 (s, 1H), 7.58 (m, 2H), 7.57 (s, 1H), 7.41 (s, 1H), 7.23 (m, 2H), 5.59 (s, 2H), 3.80 (s, 3H), 3.73 (s, 3H), 2.76 (t, $J = 7.2$ Hz, 2H), 2.62 (s, 3H), 2.32 (s, 3H), 2.14 (s, 3H), 1.75 (m, 2H), 0.95 (t, $J = 7.2$ Hz, 3H); MS m/z 454 ($M^+ + H$); FT-IR (KBr, cm^{-1}): 3061 (aromatic C−H stretching), 2963 (aliphatic C−H stretching), 1588, 1568 (aromatic C=C, C=N stretching), 1459 (aliphatic C−H bending), 1079 (C−O stretching), 834, 734 (aromatic C−H bending).

Compound 10b. ^{1}H NMR δ 8.07 (d, $J = 5.6$ Hz, 1H), 7.68 (s, 1H), 7.64 (d, $J = 7.6$ Hz, 1H), 7.57 (d, $J = 7.2$ Hz, 1H), 7.44 (s, 1H), 7.25 (m, 2H), 7.05 (d, $J = 5.6$ Hz, 1H), 5.57 (s, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H), 2.91 (t, $J = 7.2$ Hz, 2H), 2.59 (s, 3H), 1.79 (m, 2H), 0.98 (t, $J = 7.6$ Hz, 3H); MS m/z 456 ($M^+ + H$); FT-IR (KBr, cm^{-1}): 3048 (aromatic C−H stretching), 2964 (aliphatic C−H stretching), 1583, 1527 (aromatic C=C, C=N stretching), 1451 (aliphatic C−H bending), 1071 (C−O stretching), 823, 745 (aromatic C−H bending).

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Compound 10c. ^{1}H NMR δ 8.10 (d, $J = 5.2$ Hz, 1H), 7.60 (s, 1H), 7.58 (m, 2H), 7.42 (s, 1H), 7.23 (m, 2H), 7.03 (d, $J = 6.0$ Hz, 1H), 5.66 (s, 2H), 4.89 (q, $J = 8.8$ Hz, 17.2 Hz, 2H), 3.81 (s, 3H), 2.76 (t, $J = 7.6$ Hz, 2H), 2.62 (s, 3H), 2.31 (s, 3H), 1.75 (m, 2H), 0.94 (t, $J = 6.8$ Hz, 3H); MS m/z 508 ($M^+ + H$); FT-IR (KBr, cm^{-1}): 3056 (aromatic C−H stretching), 2963 (aliphatic C−H stretching), 1579, 1527 (aromatic C=C, C=N stretching), 1458 (aliphatic C−H bending), 1166 (C−O stretching), 834, 744 (aromatic C−H bending).

Compound 10d. ^{1}H NMR δ 8.03 (d, $J = 6.0$ Hz, 1H), 7.61 (d, $J = 7.2$ Hz, 1H), 7.58 (s, 1H), 7.55 (d, $J = 7.2$ Hz, 1H), 7.41 (s, 1H), 7.23 (m, 2H), 6.88 (d, $J = 5.2$ Hz, 1H), 5.60 (s, 2H), 4.09 (t, $J = 6.0$ Hz, 2H), 3.80 (s, 3H), 3.48 (t, $J = 6.0$ Hz, 2H), 3.24 (s, 3H), 2.77 (t, $J = 7.6$ Hz, 2H), 2.62 (s, 3H), 2.27 (s, 3H), 1.97 (m, 2H), 1.75 (m, 2H), 0.95 (t, $J = 7.2$ Hz, 3H); MS m/z 498 ($M^+ + H$); FT-IR (KBr, cm^{-1}): 3038 (aromatic C−H stretching), 2960 (aliphatic C−H stretching), 1579, 1524 (aromatic C=C, C=N stretching), 1459 (aliphatic C−H bending), 1090 (C−O stretching), 832, 730 (aromatic C−H bending).

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